CA 125 and Epithelial Ovarian Cancer: Role in Screening, Diagnosis, and Surveillance

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Abstract

CA125 (carbohydrate antigen 125) provides useful information for patients with a known diagnosis of ovarian cancer, but as a solitary value it is of limited use in screening in the general population. It is reasonably used during the treatment for ovarian cancer and predicts disease status in this setting. While it is often used in posttreatment surveillance, one well-performed randomized trial suggests that following CA-125 levels in asymptomatic women treated for ovarian cancer with curative intent has a negative impact on quality of life with no subsequent survival advantage. Although CA 125 has been used clinically for over 20 years, its use in some settings is still poorly defined, and the social and emotional impact of this test on patients is immense. This article summarizes the most recent research and guidelines surrounding all uses of CA 125 with regard to ovarian cancer, including screening, diagnosis, surveillance, and quality of life. Information was collected from a systematic review of published literature about CA 125 in the last 5 years using the PubMed database. The Appendix is a patient-focused summary of the role of CA 125 in ovarian cancer for patient reference during the treatment process.

Key words: ovarian cancer, tumor markers, CA 125, HE4, cancer screening, cancer surveillance, cancer diagnosis

Introduction

Each year, over 20,000 women in the United States will be diagnosed with ovarian cancer, and more than 14,000 women will have died of the disease in the year 2014.[1] Although it accounts for only 3% of malignancies in American women, ovarian cancer is the fifth most deadly cancer across cancer types, and the most fatal of the gynecologic malignancies.[2] One of the holy grails in gynecologic oncology is an effective method for screening, which would hopefully identify the disease in its earliest and most curable stage. Unfortunately, effective screening modalities have not been identified, and as a result, ovarian cancer is often not detected until late stages, with an overall 5-year survival of 44%.[3]

Central to the evaluation for and the management of ovarian cancer is the serum tumor marker carbohydrate antigen 125 (CA 125, discovered initially by Bast and colleagues in 1983). CA 125, also known as mucin 16 (muc 16), is a transmembrane glycoprotein derived from epithelium of coelomic and Müllerian origin. The extracellular membrane domains of CA 125 bind to antibodies to render quantitation of levels for clinical use.

In the original study on CA 125, Bast et al[4] reported that only 1% of healthy donors had a CA 125 level greater than 35 U/mL, and only 0.2% of healthy donors had a CA 125 level greater than 65 U/mL. Thus, 35 U/mL was accepted as a cutoff for the upper limit of normal (ULN) for CA 125 levels in the first-generation CA 125 assays. (More contemporary assays now accept a lower threshold for normal at 20 U/mL.[5]) Clinical labs typically use an immunoassay using 2 monoclonal antibodies with specificities against CA 125's two major antigenic domains, OC125 and M11.[5]

For women with ovarian cancer, CA 125 levels were found to correlate with tumor burden in 93% of cases.[4] However, even within the original study, elevations in CA 125 were not exclusive in ovarian cancers; patients with malignancies of other origins, including breast, lung, and gastrointestinal, had an elevation in CA 125.

The purpose of this article is to review the role of CA 125 testing in all of its domains related to epithelial ovarian cancer, including its role in screening, diagnosis, measuring treatment response, impact on treatment decisions, and surveillance of women in clinical remission. This article will also highlight studies that have shaped how gynecological oncology is practiced. In addition to this scholarly review, an Appendix has been created for patient education about CA 125 and how it is used to manage cancer.

Sources and Study Collection

Information for publication was collected from a systematic review of published literature on CA 125 in the past 5 years and cited in the National Library of Medicine (PubMed). We

included articles in which the primary objective was to evaluate CA 125 and its role in screening, diagnosis, follow-up, or surveillance. The following key words were used: "CA 125" and "screening," "diagnosis," "surveillance," "treatment response," "anxiety," and "secondary cytoreductive surgery." Additionally, a review of landmark descriptive studies and clinical trials related to CA 125 were included. The search was limited to data on human subjects. The articles were collected from August 2013 to October 2014.

Practical Application

- Every year, over 20,000 women in the United States will be given the diagnosis of ovarian cancer.
- Although CA 125 has been used clinically for over 20 years, its use in some settings is still poorly defined.
- The social and emotional impact of this test on patients is immense.
- A firm understanding of all arenas in which CA 125 is used is essential for treating patients with ovarian cancer.
- This manuscript provides a succinct review of all uses of CA 125 related to ovarian cancer and how it affects patients emotionally.
- The Appendix provides a rare patient-focused summary of CA 125 for patient reference.

Screening

CA 125 cannot adequately be characterized as a screening test because of the overall low incidence of ovarian cancer in the general population and the risk of a false-positive result.[4,6,7] The latter was recognized early on in the original study by Bast et al,[4] where approximately 1% of the healthy population had a CA 125 greater than 35 U/mL. The ineffectiveness of CA 125 as a screening test was best illustrated in the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial, which included over 28,000 women aged 55 to 74, all of whom underwent screening for ovarian cancer using an annual CA 125 blood test and transvaginal ultrasound.[6] Of all women screened, only 402 (1.4%) had an elevated CA 125 level. Throughout the course of the study, only 29 malignant neoplasms were diagnosed, 16 of which were associated with an elevated CA 125. However, 14 of 16 cancers were advanced at diagnosis despite screening. In addition, patients were subject to extra evaluations, and in some cases, surgical evaluation by means of exploratory laparotomy. Indeed, the authors cite that among surgeries to evaluate abnormal CA 125 levels, 1 cancer was found for every 3.9 surgeries.

When the data were re-analyzed based on a categorization of women as high- and low-risk based on CA 125 and ultrasound findings, the detection rate of ovarian cancer was improved for those at high risk, although false-positive results were still reported.[7] A prospective evaluation of this risk stratification method would be required before wider acceptance of this technique in clinical practice.

As a screening test, the positive predictive value of CA 125 is less than 4% (based on the data from the PLCO trial), which is unacceptably low for a screening test.[6] This is especially true when follow-up diagnostic procedures are invasive and carry a significant risk to the patient. In light of these and other data, the US Preventive Services Task Force gives screening for ovarian cancer with CA 125 its lowest ranking, a grade D recommendation, indicating that there are no benefits from the use of CA 125 as a screening test.[8]

Although the role of CA 125 as a screening test is not supported, other research suggests that following serial changes of CA 125 may be more effective than seeing whether CA 125 is raised beyond the ULN. The data on serial CA 125 measurements is supported by the work of Skates,[9] who hypothesized that each woman has her own baseline CA 125 and will have variation around that baseline, and that further evaluation may be indicated when there is a rise outside of this normal variation.

Using these principles, the Risk of Ovarian Cancer Algorithm (ROCA) was developed using serial CA 125 levels, age, and statistical risk of having a change point (rapid rise in CA 125 above baseline).[9] After each new CA 125 level is drawn, it can be incorporated into the algorithm, and the patient's risk recalculated. For example, an intermediate ROCA risk in otherwise unaffected women would mandate a repeat CA 125 level measurement in 3 months, while an elevated risk warrants a transvaginal ultrasound. In women of higher risk, as in personal or family history of *BRCA*-related cancers, an intermediate ROCA risk warrants transvaginal ultrasound, and an elevated ROCA risk warrants a consult with a gynecological oncologist.

Currently, there are 5 large-scale trials in the United States and Great Britain using the ROCA model to assess its efficacy in ovarian cancer screening. In a 2013 study by Pinsky et al,[10] the ROCA algorithm was applied to the data from women in the intervention arm of the PLCO trial. Data were analyzed two ways: "best-case scenario," in which all ovarian cancers detected earlier with ROCA were presumed to have survived; and "stage shift," in which cancers detected earlier via ROCA were presumed to have been at an earlier stage, and stage-specific mortality rates were applied. This analysis showed no statistically significant reduction in mortality based on application of ROCA to the PLCO data, but fatal cases of ovarian cancer in the PLCO data set were actually quite rare (n = 132). Results from studies designed specifically to use the ROCA algorithm, such as the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), better assess this application for CA 125 as a screening method.

Although the data do not support CA 125 as a screening test in the general population, women with *BRCA1* and *BRCA2* mutations have been advised to pursue screening with CA 125 and transvaginal ultrasound starting between age 30 and 35 years, or 5 to 10 years before the onset of cancer of their family member for women with a known *BRCA* mutation.[11] While the American College of Obstetrics and Gynecology (ACOG) supported this, ACOG also acknowledged the lack of data supporting the use

of CA 125 in screening for ovarian cancer.[11] Completed clinical trials such as Gynecologic Oncology Group 199 trial (GOG-199) and the UKCTOCS trial will further inform the benefits of screening these patients.

CA 125 for Diagnostic Purposes

The positive predictive value of CA 125 in women with an adnexal mass is 35% to 91%, and the negative predictive value ranges between 67% and 90%.[12] The sensitivity of CA 125 in distinguishing between benign and malignant masses ranges between 61% and 90%, while specificity ranges between 35% and 91%.[12] The wide variation in these values is due to different inclusion criteria for premenopausal women across studies.

Although few studies have looked at the role of CA 125 in the diagnosis of an adnexal mass in pre- versus postmenopausal women, it is generally accepted to be a better marker in postmenopausal women, probably because ovarian cancer is a more common diagnosis in these patients. The discrepancy in sensitivity and positive and negative predictive value of CA 125 between these populations was reported as early as 1989, in a study of 158 women of all ages with ovarian masses.[13]

In 2007, the results of the International Ovarian Tumor Analysis were published.[14] This was a multicenter prospective study of 1066 patients with persistent adnexal masses who underwent transvaginal ultrasound and CA 125 testing. In women with benign masses, there were significantly greater elevations in CA 125 among premenopausal women versus postmenopausal women. Additionally, there were greater elevations in CA 125 among postmenopausal women with malignant masses compared with premenopausal women with malignant disease, which may be partially explained by differences in tumor histology.

In addition, in 2007, ACOG published a practice bulletin outlining the appropriate steps in diagnosis of adnexal masses, both symptomatic and those found incidentally.[12] Measurement of CA 125 was supported as an essential piece of this work-up, although its clinical utility varied by whether or not a patient was premenopausal. CA 125 is elevated in 80% of women with epithelial ovarian cancer, and, therefore, ACOG recommends that postmenopausal women with an adnexal mass with any elevation in CA 125 levels be referred to a gynecologic oncologist; in contrast, referral of premenopausal women is indicated only for those with a "significantly elevated" CA 125.

CA 125 and Monitoring Response to Treatment

Clinical research has evaluated the potential predictive value of CA 125 for women undergoing cytoreduction. In 2000, Chi[15] reported a study of 100 women with stage 3 ovarian cancer who underwent cytoreduction. Of those with initial CA 125 values greater than 500 U/mL, only 22% had an optimal cytoreduction (no residual tumor greater than 1 cm remaining), versus 73% of patients with initial CA 125 values less than 500 U/mL. This study showed that CA 125 had 73% sensitivity and 78% specificity in predicting optimal cytoreduction, and other studies have yielded similar results.[15,16] The relatively low sensitivity and specificity of CA 125 in this capacity have precluded its routine use in surgical decision making for newly diagnosed patients.

For women with ovarian cancer, the response to active treatment may be monitored using CA 125, particularly if it was elevated at the time of diagnosis.[17] Using the criteria set forth by the Gynecologic Cancer Intergroup (GCIG), a response is defined as a 50% reduction in CA 125 maintained for at least 28 days. While this definition was originally developed for monitoring CA 125 levels in women with recurrent disease, it has also been applied to women undergoing first-line therapy. The initial response criteria came from the North Thames Ovary Trial, a study of 277 women that compared maintenance radiotherapy with carboplatin. The response definition from this study was then applied to 2 other clinical trials (North Thames Ovary Group study of 5 vs 8 courses of chemotherapy and GOG-97), for a total of 620 patients. Of these 620 patients, only 2 patients met the definition of CA 125 response at the time of clinical progression.[18]

In 2011, the data from the OVA-301 study, a large phase 3 trial, were used to assess the utility of CA 125 to monitor response to chemotherapy and predict progression-free survival (PFS) in patients with recurrent ovarian cancer.[19] When compared with the standard of radiographic response defined by RECIST, decline in CA 125 had both high positive and negative predictive values (90% to 92% and 89% to 90%, respectively), suggesting that CA 125 could potentially be used as a surrogate marker of treatment response as opposed to relying on CT imaging.

A focus of multiple studies has been the prognostic value of CA 125 nadir level after initial treatment of ovarian cancer with debulking surgery and chemotherapy. Most recently, van Altena and colleagues[20] followed 331 women in clinical remission after initial therapy, and found that women with CA 125 nadirs less than 5 U/mL had a longer PFS (median, 82 months vs 26 months) and greater overall survival (OS; median, 46 months vs 42 months). In a multivariate analysis, CA 125 nadir effect was found to be independent of FIGO stage as a predictor of PFS. Additionally, in a small trial, CA 125 nadir levels less than 10 U/mL have been associated with greater PFS in patients undergoing paclitaxel maintenance therapy.[21]

In the setting of recurrent disease, the CALYPSO trial of carboplatin with either paclitaxel or pegylated liposomal doxorubicin for women with platinum-sensitive ovarian cancer was the first to incorporate CA 125 doubling, along with radiological evidence according to RECIST, as a criterion to detect progression of recurrent ovarian cancer.[22] In this study, only a minority of patients (28%) had a rising CA 125 as the first sign of progressive disease. Among these patients, the time between CA 125 doubling and radiographic or symptomatic progression was

2 months. However, change in management strategy was most commonly delayed until radiographic or symptomatic progression was evident, raising questions regarding the applicability of changes in CA 125 for therapeutic decision making.

CA 125 and Surveillance

It has long been established that CA 125 levels will rise several months prior to clinical recurrence of ovarian cancer.[23] Thus, guidelines for women following initial treatment for ovarian cancer include CA 125 testing as a part of routine follow-up care.[24] However, whether this should be a component of standard follow-up has recently been questioned.

This questioning is based on the results of the Medical Research Council (MRC) 05 trial, in which 1442 women who were in complete remission after first-line platinum-based chemotherapy and a normal posttreatment CA 125 were enrolled.[23] Each of these patients had her CA 125 checked every 3 months, but both patients and physicians were blinded to the results. Once patients had an elevation in CA 125 to twice the ULN (≥ 70 U/mL), they were randomized to either an early-treatment group (in which case their results were released to them and their clinicians) or a delayed-treatment group (in which case they remained blinded to the results). Compared with women on the delayed-treatment arm, those in the early-treatment group started chemotherapy an average 4.8 months earlier, reported significantly more side effects, and had poorer quality of life. In addition, early initiation of treatment had no impact on OS.

Largely based upon this data, the National Comprehensive Cancer Network (NCCN) now recommends that measurement for CA 125 be individualized rather than routinely performed following first-line treatment for ovarian cancer.[25] This is a change from the 2008 guidelines that called for CA 125 testing at every follow-up visit, 4 times per year for 2 years, and twice per year for another 3 years.

The potential cost savings of not performing scheduled CA 125 testing was recently demonstrated by Armstrong et al,[26] where the estimated cost to follow patients diagnosed over 2 years (approximately 22,000 patients) using 2008 NCCN guidelines was approximately $32.5 million. If each patient gets just 1 CT scan, the cost nearly doubles to $58 million. In an era where value and quality are becoming more important in the treatment of patients with cancer, therapy based solely on rise in CA 125 is defined as a "low-value practice," meaning that it has a significant cost without substantial benefit.[27]

Although measurement of CA 125 in patients in clinical remission following primary treatment may not lead to better outcomes, some data suggest that monitoring the rate of rise of CA 125 in this population may be of prognostic value. In a small study of 52 women being monitored after completion of primary therapy, those with a gradual rise in CA 125 had significantly longer PFS than those women with rapid CA 125 rises (median, 22.96 vs 14.07 months).[28]

Despite these data, some argue that there may be patients who could potentially benefit from detecting a recurrence of disease just by elevation in CA 125 level, particularly if they would be candidates for secondary surgical cytoreduction. For example, Wang and colleagues[29] have identified a CA 125 level of greater than 1.68 times the nadir as a cutoff for relapse, with a sensitivity of 82.9% and specificity of 85.6%. Of the 193 patients in this study with clinical recurrence, 111 had a CA 125 level greater than 1.86 times the nadir prior to the presentation of clinical symptoms, with an average lead time of 31 days. In Cox proportional hazard models, an increase in CA 125 level at relapse was an independent predictor of both OS (P = .004) and PFS (P = .002), and multivariate analysis showed that secondary cytoreduction was an independent predictor of both OS (P = .002) and PFS (P = .01).

Currently, the NRG Oncology group is conducting GOG-213 to assess the role of secondary cytoreduction in patients with ovarian cancer (NCT00565851). In this study, patients with a rising CA 125 and disease recurrence on imaging are randomized to surgery or no surgery. All patients receive chemotherapy, with randomization to either carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab. The results of this study have the potential to make monitoring of CA 125 invaluable in the surveillance of patients. Results are due to be published in the coming years; however, recruitment has been slow, and results may be delayed.

CA 125 and Quality of Life

For all cancer survivors, making the transition from intensive treatment to regular outpatient follow-up is challenging. This is especially true for those completing treatment for ovarian cancer, as the risk of recurrence is extremely high. All providers who treat patients with ovarian cancer have encountered women in whom preoccupation with their CA 125 level negatively influences their quality of life, with cyclical rises and falls in anxiety surrounding follow-up appointments and blood draws.

In a study of 126 women with epithelial ovarian cancer, Parker and colleagues[30] used surveys to measure knowledge about ovarian cancer, levels of CA 125 preoccupation, depression symptoms, and anxiety symptoms. Overall, the women, all of whom were undergoing treatment for ovarian cancer, scored low on the knowledge section, which included questions about CA 125 (mean score of 5.3 out of possible 10). Women did tend to understand that CA 125 was a tumor marker found in blood and that large increases indicate that cancer may have returned. However, there was less understanding of the meaning of smaller increases in CA 125 level. While there was a positive correlation between higher knowledge score and CA 125 preoccupation, among patients with high CA 125 preoccupation scores, those with low knowledge scores were significantly more likely to be depressed. These data suggest that knowledge about ovarian cancer

and CA 125 may be protective against depression, but does not prevent preoccupation with CA 125 levels.

In another study, by Hipkins and colleagues,[31] levels of anxiety and depression were measured in patients with ovarian cancer at the time of their last chemotherapy and at 3-month follow-up visits. At the time of the first measurement, 38% of women had clinically pathologic anxiety and 27% had clinical depression. Three months later, the rates of anxiety increased to 47% of participants, and depression rates fell to 19%. These results are likely reflective of the challenges of transitioning from intensive treatment to a new posttreatment life. The sharp rise in anxiety at the 3-month mark suggests that the more appropriate time to have an informed discussion with patients about the use of CA 125 in their follow-up care is actually immediately following the final chemotherapy, not at the first follow-up visit, when anxiety levels tend to be higher.

How best to disseminate accurate information so patients can make informed decisions is an important area of needed discussion. In a meta-analysis, Friedman et al[32] compiled data analyzing the efficacy of written materials to enhance patient education. They found that generalized materials written by physicians tended to increase patient satisfaction and recall of material. When compared with verbal education alone, the addition of written materials significantly improved patient comprehension of educational material. Written material also provides a source of physician-reviewed information that patients may refer to in the future. The ability to reference educational materials over time is especially applicable to topics such as CA 125 because its role changes over the course of diagnosis and treatment of ovarian cancer.

Future Directions

CA 125 continues to be a topic of investigation among ovarian cancer researchers. This research includes analyzing CA 125 levels with other biomarkers, such as human epididymis protein 4 (HE4) and mesothelin (MES). HE4 is a glycoprotein expressed in normal female reproductive tissues that is overexpressed in reproductive cancer. HE4 levels are less sensitive to the menopausal status of the patient.[33] In one study, when compared with CA 125 as a tool for detecting ovarian cancer, HE4 was more sensitive (90% vs 83%) and specific (95.0 vs 85.0%), and had higher positive (93.1% vs 80.7%) and negative (92.7% vs 87.2%) predictive values.[34] When the levels of these 2 biomarkers are combined into the Risk of Ovarian Malignancy Algorithm (ROMA), the combined sensitivity and specificity of detecting an ovarian cancer using CA 125 and HE4 have been reported as 76% and 95%, respectively.[33] Trials are currently under way to investigate the use of CA 125 and HE4 as targets of antibody therapy. Similarly, mesothelin is an antigen found on normal mesothelium that is also elevated in ovarian cancer. In diagnosis of ovarian masses, the combination of MES and CA 125 measurements have been 98% sensitive in detecting malignancy.[33] Both of these tumor markers, along with others, are under investigation for clinical use, and their utility remains to be seen.

Additionally, various prediction models involving CA 125 are in development. A study by Suidan and colleagues[35] created a preoperative scoring system using CA 125 and CT scan to predict when ovarian cancer is likely to be suboptimally reduced. Although results are modest, the idea that a CA 125 level can be used in conjunction with other measures to predict ovarian cancer course is a fast growing one. In addition, algorithms that use multiple levels of CA 125 over time, as opposed to a singular value, are in production. One such study used data from the CALYPSO trial and showed that longitudinal change in CA 125 between start of treatment and 6 weeks afterward is predictive of PFS.[36] Another study used data from the PLCO study and applied the parametric empirical Bayes longitudinal screening algorithm to CA 125 levels over time. This would have allowed for earlier diagnosis (on average, 10 months) in 20% of the women in the study compared with the single threshold of CA 125 greater than 35 U/mL.[37]

Conclusion

Although CA 125 has now been used clinically in patients with ovarian cancer for more than 20 years, its role is still not clearly defined in all settings, and its utilization continues to evolve. This leads to challenges for physicians with regard to using CA 125 to provide optimal care and maintain a quality of life that is acceptable to the patient. Central to patient education about ovarian cancer should be a discussion about the benefits and drawbacks of using CA 125 in each domain. This discussion is essential to maintaining the autonomy that oncology patients so deeply deserve.

Following this article is an Appendix containing patient education information that can be used with patients to facilitate a discussion about CA 125. A PDF for distribution to patients can be downloaded at www.ajho.com/go/Ovarian. It can serve as a resource for patients as their treatment progresses. In understandable language, it outlines the use of CA 125 in all of its settings. Although it is geared toward women with a recent diagnosis or recurrence of ovarian cancer, it also provides information about screening and diagnosis, as recently diagnosed women will have questions about these topics with regard to themselves and their loved ones. It is the goal of this review and patient education information to begin an effort to ensure that patients are adequately informed with physician-approved materials so that they can make well-informed decisions for themselves.

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CA 125 and Ovarian Cancer

Information for Patients

Introduction

- CA 125 is a marker in the blood that is known to be elevated in women with ovarian cancer, but also in people with other medical conditions and in some healthy people.
- CA 125 is a "tumor marker" since it can correlate with the amount of tumor growth in a woman with a known diagnosis of ovarian cancer.
- When it was discovered in 1983, 35 U/mL was made the normal value, since only 1% of a large group of healthy people had a CA 125 greater than 35 U/mL.
- CA 125 is not a perfect test for ovarian cancer, and its use is controversial in some settings.

CA 125 and Screening for Ovarian Cancer

- In medicine, a screening test is one that is used to detect a precursor or early form of a disease so that it can be treated before the disease progresses and becomes life-threatening. (Examples include mammograms for breast cancer and Pap smears for cervical cancer.)
- Screening tests are given to people who have no symptoms.
- CA 125 should not be considered a screening test because:
  - CA 125 can be elevated in many other conditions, so some women without ovarian cancer can have an elevated CA 125.
  - Many women with an early ovarian cancer do not have an elevated CA 125.
- Research has shown that checking CA 125 levels in all women does not find very many ovarian cancers, but it does lead to many women having unnecessary surgery and other testing procedures to investigate the high CA 125.

CA 125 and Diagnosis of an Ovarian Mass

- CA 125 can be useful when an ovarian mass is felt on exam or seen on ultrasound and the physician is unsure whether it is ovarian cancer.
- The CA 125 test is better for women who have gone through menopause because they do not have as many non-ovarian cancer conditions that can raise a CA 125 level.
- It is recommended that all women with an ovarian mass get a CA 125 level test:
  - Postmenopausal women should be sent to a gynecologic oncologist if their level is over 35 U/mL.
  - Premenopausal women should not see a gynecologic oncologist unless the level is very high, since they are more likely to have a noncancer cause of an elevated CA 125.

CA 125 and Monitoring Response to Ovarian Cancer Treatment

- While undergoing treatment for ovarian cancer, CA 125 levels are checked often to help doctors determine whether the cancer is responding to treatment (surgery and chemotherapy).
- A good response to treatment is when the CA 125 level drops to half of its highest level.
- The cancer is getting worse or progressing when the CA 125 level remains double the normal value or double the lowest level it has ever been.
- During treatment, doctors should not rely solely on the changes in CA 125. Treatment changes or adjustments should be based on physical exam and imaging evaluation (such as computed tomography [CT] scans), with additional information gained by changes in the CA 125 levels.

CA 125 and Surveillance

- Surveillance is the time after ovarian cancer has been successfully treated the first time.
- Many women worry a lot about their CA 125 level rising and feel anxious before every visit.
- CA 125 levels can rise in the blood prior to recurrent cancer showing up on a scan or causing symptoms, such as pain or bloating.
- There appears to be no survival benefit to testing CA 125 in someone without symptoms or clinical suspicion that cancer has recurred. Also, there are more side effects in tested patients, as they spend more time on chemotherapy since relapses are picked up sooner.
- However, the preference of the woman undergoing surveillance after treatment for ovarian cancer needs to be taken into account. Studies show that during surveillance:
  - Some women would rather not know that their cancer has come back until it causes symptoms, and pursue treatment at that time.
  - Some women feel better knowing right away when their CA 125 rises, and want to start treatment again before they have any symptoms.
  - Both types of patients live the same amount of time.

For printouts, please download the PDF at www.ajho.com/go/Ovarian

Appendix to: Pepin K, del Carmen M, Brown A, Dizon, DS. CA 125 and epithelial ovarian cancer: role in screening, diagnosis, and surveillance. Am J Hematol Onc. *2014;10(6):22-29. Reprinted with permission of the* American Journal of Hematology/Oncology. *Copyright 2014.*